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Using a structured medical note for determining the safety profile of anthrax vaccine for US soldiers in Korea

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Abstract

Selected military personnel are immunized with an FDA-licensed anthrax vaccine unless there are clinical contraindications. The objective of this analysis is to capture the experience of soldiers receiving anthrax vaccine to assist in better patient-provider communication and clarify the safety profile of the vaccine in this population as a quality-assurance initiative. Between August 1998 and July 1999, 2824 soldiers immunized against anthrax at one military clinic completed a structured medical note that was reviewed by a clinician. Female gender, prior vaccine-associated adverse events, and medication use were significantly related to higher reports of adverse events. All reported immediate consequences resolved.

Keywords: Anthrax vaccine; Vaccine safety profile; Adverse event reporting; Cohort study; Structured medical note; Outcome analysis

1. Introduction

Weaponized anthrax has been recognized as a biowarfare and bioterrorist threat, against which there is a safe and effective vaccine [1–8]. The anthrax vaccine adsorbed (AVA) mass immunization program was initiated in August 1998 for all US Forces in Korea (USFK). Mass immunization program guidelines were formulated and published [9,10]. Guidelines called for all personnel immunized to have that immunization documented in their paper medical record and in an automated immunization tracking system (ITS). The ITS tracked dose of vaccine administered, manufacturer and lot number, along with all permanent and temporary medical exemptions and administrative deferrals. Any individual with a vaccine-related question or potentially related problem was encouraged to seek medical attention that would be documented in the medical record. A vaccine adverse event reporting system (VAERS) report was to be generated for any problem believed to be vaccine-associated and that resulted in hospitalization, an emergency visit, 24 h of lost duty or an unusual event of concern to either health care provider or soldier. Severe adverse events where it might be decided to discontinue further immunizations were also documented through VAERS. As a result of policy and guidance, the implementation plan emphasized compliance to the FDA package insert to include the immunization schedule of a six shot primary series to be administered subcutaneously (SC) at 0, 2, 4 weeks and 6, 12, 18 months; with an annual booster thereafter [11]. Commanders would be warned when any soldier was 2 weeks late for any scheduled immunization.

Medical personnel at all immunization sites were expected to make correct immunization decisions. Remote military clinics share many features of those settings in which vaccine outreach programs occur, such as limited professional staff serving large numbers of patients, while ensuring thorough documentation and quality control. Using lessons learned from a comprehensive business process re-engineering project, a structured anthrax immunization medical note (AIMN) was designed for use by one remote immunization site [12–19]. The AIMN was structured to

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enhance provider-soldier communication, support provider decision-making, and allow aggregate data analysis for outcome evaluation.

This paper presents the outcomes of this continuous performance improvement program, emphasizing patient-reported frequencies of local and systemic adverse events. Preliminary findings of gender differences in reporting adverse events were published in 2000 and 2001 [20–23]. Presentation of these findings were also considered in the 2000–2002 Institute of Medicine (IOM) study that assessed the safety and efficacy of the anthrax vaccine used in the military [24]. Additional records added to the database are analyzed to determine if the initial differences reported continue to be observed in a larger population. Because the package insert and implementation instructions required an assessment of specific current medications and health status, those dimensions were reflected on the AIMN and also became available for analysis.

2. Methods

2.1. Subjects

In September 1998, soldiers served by the Camp Casey Troop Medical Clinic (TMC) began their immunization series. A single AVA lot, FAV017, was used for all immunizations. Almost all soldiers served a 1-year tour and most were in their early 1920s. Each soldier belonged to a unit that was scheduled for immunization clinic every 2 weeks so that each soldier could be immunized according to the licensed immunization schedule, every 2 weeks for the first three shots, and 5 months after the third shot. Because of normal length of time assigned in Korea, most soldiers would have departed by the time the fifth shot was scheduled. Both commanders and soldiers were warned when they were 2 weeks late, so there was high motivation to be immunized according to the licensed immunization schedule. In general, soldiers assigned to Camp Casey were expected to be physically healthy, and without any disabling medical conditions. Any soldier who became significantly ill during their tour would be sent to Seoul for additional care and would not be expected to remain at Camp Casey while significantly ill. Soldiers were informed about the anthrax disease threat and the vaccine using the AIMN as part of a quality-improvement standardization initiative.

2.2. Data collection

The 18th Medical Command Preventive Medicine Consultant (KH) generated a standardized form, AIMN, using Teleforms® version 6 (Fig. 1) for use by health care providers and technicians at the Camp Casey TMC. Questions addressed current health status, medications, symptoms experienced, and consequences of symptoms after the previous dose, emphasizing items mentioned in the AVA package insert. Soldiers completed most fields on the AIMN before vaccination, including demographics, gender (with pregnancy status, if female), active health problems, current medication use, and adverse event experience with consequences after the previous anthrax vaccination. The provider reviewed the form and documented whether the immunization was administered. AIMNs were secured and stored in the TMC until after the third immunization. Collected AIMNs were forwarded to the 18th Medical Command Preventive Medicine Section, Yongsan, Korea, from December 1998 to July 1999 for review and analysis. Information on the AIMN was extracted into an SPSS® database.

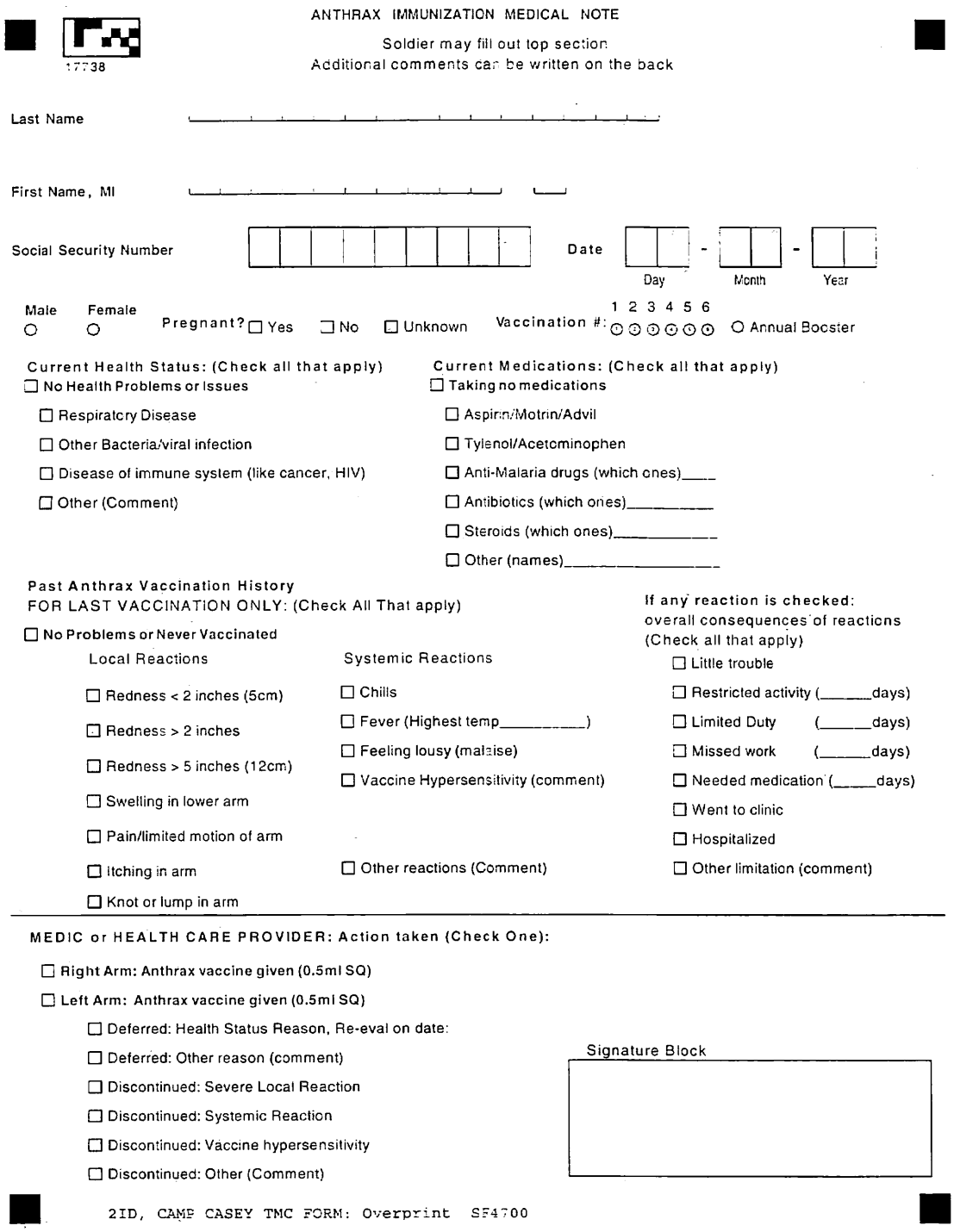
2.3. Data analysis

Under an analysis protocol approved by the Walter Reed Army Medical Center's Department of Clinical Investigation, data collected between September 1998 and July 1999 were analyzed with gender stratification for rates of reported adverse events. A health problem at the time of immunization was defined as any checked or other illness written on the AIMN present at the time of vaccination. Current medication at the time of vaccination was defined as any checked or other medication written on the AIMN.

An adverse event to AVA was defined as a report of local reactions consisting of redness, knot, swelling, or pain; systemic events defined by chills, feeling lousy (malaise), fever, anaphylaxis; or other reaction the soldier or medical personnel believed to be related to the immunization. An indicator variable for "any adverse event" was generated to reflect whether the soldier had reported one or more adverse events for use in multivariate analysis.

Consequences were defined as restricted activity, limited duty, missed work, a clinic visit, medication use, or hospitalization following immunization. For each consequence, the soldier could mark its duration. The AIMN also allowed either soldier or clinician to enter other comments related to health status, medications, adverse events or consequences. Privacy and confidentiality of individual records was assured through coding of records and removal of individual identifiers after linking but prior to analysis.

Most analysis was completed using cross-tabulations and χ^2 statistics using SPSS®. Logistic regression models assessing the association between any adverse event, health problem, gender, medication, and prior adverse event utilized forward-step likelihood ratios to establish per cent variance explained by the models and odds ratios with 95% confidence intervals (CI) of significant variables. In addition, a population segmentation multivariate analysis. Answer Tree® version 1 Chi Square Automatic Interaction Detector (CHAID), was used to specifically identify populations with distinctive characteristics that would be associated with the report of any adverse event. CHAID uses maximal statistical differences between variables to create population segmentation models [25,26].



ANTHRAX IMMUNIZATION MEDICAL NOTE

Soldier may fill out top section
Additional comments can be written on the back

17738

Last Name

First Name, MI

Social Security Number

Date Day - Month - Year

Male ○ Female ○ Pregnant? ☐ Yes ☐ No ☐ Unknown Vaccination #: 1 2 3 4 5 6 ○ ○ ○ ○ ○ ○ ○ Annual Booster

Current Health Status: (Check all that apply)
☐ No Health Problems or Issues
☐ Respiratory Disease
☐ Other Bacteria/viral infection
☐ Disease of immune system (like cancer, HIV)
☐ Other (Comment)

Current Medications: (Check all that apply)
☐ Taking no medications
☐ Aspirin/Motrin/Advil
☐ Tylenol/Acetominophen
☐ Anti-Malaria drugs (which ones)____
☐ Antibiotics (which ones)_____
☐ Steroids (which ones)_____
☐ Other (names)_____

Past Anthrax Vaccination History
FOR LAST VACCINATION ONLY: (Check All That apply)
☐ No Problems or Never Vaccinated

Local Reactions
☐ Redness < 2 inches (5cm)
☐ Redness > 2 inches
☐ Redness > 5 inches (12cm)
☐ Swelling in lower arm
☐ Pain/limited motion of arm
☐ Itching in arm
☐ Knot or lump in arm

Systemic Reactions
☐ Chills
☐ Fever (Highest temp_____)
☐ Feeling lousy (malaise)
☐ Vaccine Hypersensitivity (comment)
☐ Other reactions (Comment)

If any reaction is checked: overall consequences of reactions (Check all that apply)
☐ Little trouble
☐ Restricted activity (_____days)
☐ Limited Duty (_____days)
☐ Missed work (_____days)
☐ Needed medication (_____days)
☐ Went to clinic
☐ Hospitalized
☐ Other limitation (comment)

MEDIC or HEALTH CARE PROVIDER: Action taken (Check One):
☐ Right Arm: Anthrax vaccine given (0.5ml SQ)
☐ Left Arm: Anthrax vaccine given (0.5ml SQ)
☐ Deferred: Health Status Reason, Re-eval on date:
☐ Deferred: Other reason (comment)
☐ Discontinued: Severe Local Reaction
☐ Discontinued: Systemic Reaction
☐ Discontinued: Vaccine hypersensitivity
☐ Discontinued: Other (Comment)

Signature Block

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Fig. 1.

3. Results

A total of 6489 AIMNs, representing information on 2824 unique individuals, 2214 male and 610 female, receiving between one and four immunizations were used in this analysis. Fig. 2 summarizes the numbers and percent of men and women, and the percent of records that could be linked to a record of previous immunization at the Camp Casey TMC. A unique soldier identification number was used to link records. Non-linkage is expected to occur whenever the soldier was immunized outside of this specific immunization clinic, such as at a reception station upon first arrival into

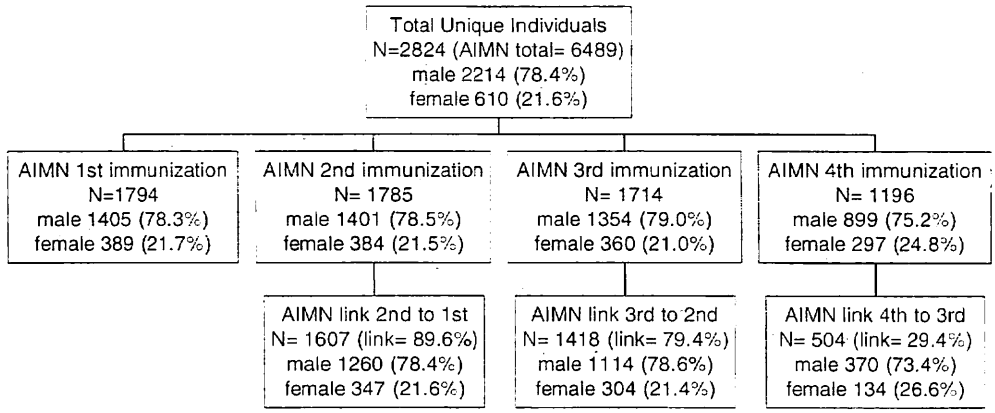

Fig. 2. Breakdown of anthrax immunization medical notes representing 2824 individuals receiving any one or more of the first four anthrax vaccines at one troop medical clinic.

country or if at another clinic when an immunization was due. Expected rotations, resulting in new people arriving at Camp Casey and others completing their 1-year tour is reflected in the higher number of record linkages on the start dates, between September and November, and lower number of linkages 5 months later. To describe adverse events and consequences related to gender, all collected notes not missing the critical dependent variable could be used. Thus, 1781 AIMNs reflect knowledge whether an adverse event occurred following the first immunization, 1706 AIMNs reflect the second, and 1196 AIMNs reflect the third. Since the second (or follow-up) note is needed to get self-report data on adverse events and consequences following immunization, while information about health status and medication at the time of immunization is on the initial note; for health status, 1601 AIMNs are linked to report on the first immunization, 1415 are linked to report on the second immunization and 503 are linked to report on the third immunization; and for medication use, 1602 AIMNs were linked; to report on the second immunization, 1405 AIMNs were linked; and to report on the third immunization, 503 AIMNs were linked.

3.1. Gender and adverse event reporting

Across all three immunizations, the range of women reporting any reaction was 59.9–67.9% while the range of men was 31.5–39.7%. Women reported more systemic and local side-effects than men (Table 1). Nodules (range 49.8–62.4% women, 21.4–28.9% men) and injection-site erythema (range 24.8–30.9% women, 11.5–13.6% men) were common. The rates of injection-site erythema exceeding 12 cm diameter ranged from 2.0 to 4.1% among women, and 0.4 to 1.1% among men. Among systemic adverse events, the greatest differences are found among the percentages of males and females reporting malaise (range 8.4–15.4% women, 3.6–6.5% men).

3.2. Health status and adverse event reporting

Those reporting minor health problems at the time of immunization were more likely to report adverse events since that vaccination, compared to those who did not report health problems (Table 2). Significant differences ($P < 0.05$) included knots, pain or limited motion, and

Table 1
Reported adverse events by gender amongst soldiers immunized

	Vaccination 1 (%)		Vaccination 2 (%)		Vaccination 3 (%)	
	Male ($N = 1398$)	Female ($N = 383$)	Male ($N = 1346$)	Female ($N = 360$)	Male ($N = 899$)	Female ($N = 297$)
Any reaction	**39.6**	**67.9**	**39.7**	**66.1**	**31.5**	**59.9**
Knot	**28.1**	**58.5**	**28.9**	**62.4**	**21.4**	**49.8**
Red <5 cm	**7.2**	**11.7**	**7.7**	**13.5**	**7.6**	**12.0**
Red >5 cm	**3.9**	**11.0**	**4.8**	**13.3**	**4.0**	**10.7**
Red >12 cm	*0.4*	*2.1*	*1.1*	*4.1*	*0.4*	*2.0*
Pain	**10.2**	**18.8**	**9.6**	**15.0**	**9.7**	**16.1**
Itching	**6.2**	**20.4**	**7.5**	**37.0**	**5.5**	**27.1**
Swelling	2.7	3.9	*3.4*	*8.6*	*2.5*	*9.4*
Malaise	**6.5**	**15.4**	**5.4**	**14.4**	**3.6**	**8.4**
Chills	**2.4**	**5.5**	1.4	3.0	1.2	3.0
Fever	1.0	2.1	*1.0*	*3.6*	**0.7**	**4.0**
Other	4.4	5.2	3.4	5.0	*0.8*	*2.7*

Comparing male and female for each vaccination reaction: $P < 0.01$ in bold. $P < 0.05$ in italic.

Table 2
Reported adverse events by health status at time of immunization

	Vaccination 1 (%)		Vaccination 2 (%)		Vaccination 3 (%)	
	Healthy ($N = 1480$)	Problem ($N = 121$)	Healthy ($N = 1325$)	Problem ($N = 90$)	Healthy ($N = 481$)	Problem ($N = 22$)
Any reaction	**45.3**	**65.3**	45.7	55.6	37.4	50.0
Knot	**34.2**	**52.9**	36.6	43.3	**27.4**	**54.5**
Any redness	14.9	21.5	17.9	18.9	15.6	22.7
Red <5 cm	8.6	12.4	9.6	5.6	10.2	4.5
Red >5 cm	5.7	8.3	6.4	8.9	*4.6*	*18.2*
Red >12 cm	0.7	0.8	1.9	4.4	0.8	0.0
Pain	**11.6**	**22.3**	**10.0**	**21.3**	9.1	22.7
Itching	**8.5**	**18.2**	14.0	20.0	*12.1*	*27.3*
Swelling	3.0	3.3	4.7	5.6	3.5	13.6
Malaise	*7.9*	*13.2*	*7.4*	*13.3*	4.0	9.1
Chills	2.8	3.3	1.9	3.3	1.5	0.0
Fever	*1.1*	*4.1*	1.6	3.3	0.6	4.5
Other	**3.8**	**16.7**	**3.4**	**11.1**	1.0	0.0

Comparing health status by vaccination reaction: $P < 0.01$ in bold. $P < 0.05$ in italic.

malaise. Of special note are the significantly higher rates of "other" adverse reactions, such as headache and flu-like symptoms, after the first two vaccinations among the group reporting minor health problems.

3.3. Medication use and adverse event reporting

For almost all types of adverse events, soldiers taking medication at the time of immunization were also more likely to report an adverse effect from the anthrax vaccine when queried several weeks or months later from receiving the first three immunizations (Table 3). Significant differences ($P < 0.05$) included knots, redness, pain, and itching. Significantly higher rates of "other" adverse reactions are reported among the group taking a medication after the first two immunizations.

When assessing specific medications, current use of NSAID medications (prompted as "Aspirin/Motrin/Advil" on the AIMN) appear to be more strongly associated with a report of an adverse event following the last immunization. Among those for whom there is follow-up AIMN adverse event information, NSAID medication are taken by 7.2% of those first immunized, 5.7% of those receiving their second immunization and 5.2% of those taking their third immunization. Across all three immunization adverse events reports, a significantly higher percentage ($P < 0.05$) vaccine recipients taking a NSAID report knots. Across the first two immunizations, a significantly higher percentage also report redness <5 cm diameter, redness <12 cm, pain, and itching. After the first immunization only, a significantly higher percentage reports fever. After the second immunization only, a significantly higher percentage reports malaise. After the third immunization only, significantly higher percentage reports chills and malaise. Extracting birth control medication (BCM), either as a pill or implant, information from other medication comments reflect that 23.1% of women who have a second AIMN note reporting adverse events to the first immunization wrote they were taking some type of

Table 3
Reported adverse events by medication use at time of immunization

	Vaccination 1 (%)		Vaccination 2 (%)		Vaccination 3 (%)	
	No meds ($N = 1245$)	Taking meds ($N = 357$)	No meds ($N = 1325$)	Taking meds ($N = 90$)	No meds ($N = 407$)	Taking meds ($N = 96$)
Any reaction	**41.3**	**66.1**	**42.3**	**62.4**	**32.9**	**59.4**
Knot	**30.3**	**54.1**	**33.1**	**52.6**	**23.1**	**52.1**
Any redness	**12.9**	**24.4**	**15.3**	**28.2**	*14.0*	*24.0*
Red <5 cm	**7.6**	**13.2**	*8.3*	*13.2*	9.6	11.5
Red >5 cm	**4.8**	**9.5**	**5.3**	**11.5**	*3.9*	*10.4*
Red >12 cm	*0.4*	*1.7*	1.7	3.5	0.5	2.1
Pain	**11.1**	**16.9**	*9.8*	*14.7*	*8.1*	*16.7*
Itching	**7.3**	**16.0**	**11.1**	**27.5**	**10.1**	**24.0**
Swelling	2.7	4.5	4.3	6.6	**2.7**	**9.4**
Malaise	*7.5*	*11.2*	**5.5**	**16.7**	3.4	7.3
Chills	2.7	3.4	1.7	3.1	1.2	2.1
Fever	1.2	1.7	1.4	2.8	0.5	2.1
Other	**3.9**	**7.9**	**3.1**	**7.0**	1.0	1.0

Comparing medication use by vaccination reaction: $P < 0.01$ in bold. $P < 0.05$ in italic.

Table 4
Logistic regression predicting anthrax vaccine adverse event(s)

Variable	Odds ratio	95% CI	Reference
Predicting side-effects to the first anthrax vaccination[a]			
Gender female	2.8	(2.1, 3.6)	Male
Taking meds	2.2	(1.7, 2.8)	No meds
Predicting side-effects to the second anthrax vaccination[b]			
Gender female	1.7	(1.2, 2.3)	Male
Rxn: first vaccination	12.2	(9.5, 15.8)	No rxn
Predicting side-effects to the third anthrax vaccination[c]			
Gender female	2.4	(1.5, 3.7)	Male
Rxn: second vaccination	5.5	(3.6, 8.4)	No rxn

Method: forward stepwise likelihood ratio; variables considered: gender, current health status (health), current use of medication (meds), reported reaction(s) to last anthrax vaccination (rxn).

[a] Number of cases included in the analysis: 1601; $R^2 = 8\%$.

[b] Number of cases included in the analysis: 1413; $R^2 = 29.4\%$.

[c] Number of cases included in the analysis: 501.; $R^2 = 19.4\%$.

BCM. Comparing women who wrote in a BCM from those who did not reflects no statistical association with a higher or lower percentage of vaccine adverse events.

3.4. Multivariate analysis

To determine the relative contribution of gender, health status, medication use, and past adverse events to anthrax vaccine in predicting the report of any adverse event to the current immunization, we built a logistic regression model with health, medication and gender as dichotomous independent variables as highlighted in Table 4. Interactions were also considered but did not contribute significantly to the model. Gender had the greatest impact on likelihood ratio for all three immunizations and was entered first into all three models. The regression using information available at the time of the first immunization results in a model in which only 8% of the variance is explained. By the time the second vaccination is given, a powerful additional variable emerges. The history of an adverse event after an anthrax immunization results in a model in which 19–30% of the variance is explained.

The same variables are used in a multivariate population segmentation analysis (CHAID). Table 5 highlights the population segmentation analysis from the same population analyzed in the regression model. To assess the relationship between any adverse event to the first immunization as reported on the second AIMN, gender, health status and medication use are evaluated from the first AIMN. Gender has the greatest effect, followed by medication. Of 199 men taking medication, 55.8% report one or more adverse events, while of the 224 women not known to be taking medication, 60.3% report one of more adverse events. To assess the relationship between any adverse event to the second immunization as reported on the third AIMN, health status, medication use and any adverse event to the first immunization are evaluated from the second AIMN. Gender is captured from any AIMN to decrease missing information related to this variable. In cases where there was no information (i.e. a missing immunization note), the adverse-event percentage was similar to the percentage of men and women generally reporting adverse events. The greatest number of men who had no adverse events are segmented by medication use, in which those using medication have a higher adverse event reporting rate (29% versus 17%). Analysis of adverse events to the third immunization segments the same variables extracting those variables from the third and fourth AIMN. This segmentation model isolates specific groups of men who have higher rates of reported adverse events and women who have

Table 5
Population segmentation analysis: any adverse reaction rate by population characteristics

Population segment (N)	Reported adverse events (%)	Gender	Other characteristics
First immunization: overall reaction rate among 1781 reports: 54.35%			
158	79.1	Female	Taking medication
224	60.3	Female	No/unknown meds
199	55.8	Male	Taking medication
1200	36.8	Male	No/unknown meds
Second immunization: overall reaction rate among 1706 reports: 45.31%			
209	81.3	Female	Rxn to last immunization
447	74.7	Male	Rxn to last immunization
57	68.4	Female	Rxn to last immunization unknown
236	33.1	Male	Rxn to last immunization unknown
94	30.8	Female	No rxn to last immunization
73	28.8	Male	No rxn to last immunization/taking meds
590	17.3	Male	No rxn to last immunization/no meds
Third immunization: overall reaction rate among 1196 reports: 38.55%			
257	64.2	Female	Rxn to last immunization or unknown
139	52.5	Male	Rxn to last immunization
39	33.3	Female	No rxn to last immunization
533	32.5	Male	Rxn to last immunization unknown
228	16.2	Male	No rxn to last immunization

Table 6
Reported consequences by gender amongst those reporting one or more adverse events

	Vaccination 1 (%)		Vaccination 2 (%)		Vaccination 3 (%)	
	Male ($N = 553$)	Female ($N = 260$)	Male ($N = 535$)	Female ($N = 238$)	Male ($N = 283$)	Female ($N = 178$)
Less active	4.5	3.1	2.8	3.8	5.7	6.7
Duty limited	*0.2*	*1.9*	0.0	0.4	0.4	1.7
Lost work	0.4	0.8	0.7	0.0	0.7	1.1
Used meds	0.2	0.8	0.2	0.0	0.0	0.6
Visited clinic	1.1	0.8	1.7	1.3	0.4	2.2
Other consequences	0.2	0.4	0.4	0.0	0.0	0.0

Comparing male and female by vaccination reaction: $P < 0.05$ in italic.

lower rates than gender specific averages as a function of past reactions to anthrax vaccine and medication use.

3.5. Consequences related to adverse events

Overall, reported adverse events appeared self-limited and to have relatively minor medical or work-related consequences. The analysis of consequences includes only those individuals who reported one or more adverse events to a given immunization. In absolute numbers, 42 of 813 (5.2%) who reported any adverse event for the first immunization also reported a medical or work-related consequence, 30/773 (3.9%) reported a consequence for the second, and 33/461 (7.2%) for the third. Table 6 reports the percent reporting different work-related and medically related consequences from the population reporting any adverse event for each of the first three immunizations highlighting the comparison between genders. With a single exception (i.e. duty limitation after the first immunization), stratifying by gender showed no statistically significant differences in reported consequences of adverse events, although in many categories, the percentage of women reporting an adverse consequence is slightly higher than men.

A single individual could report more than one consequence, such as visiting a clinic and taking medication. After the first vaccination, 42 individuals reported a total of 60 consequences. After the second vaccination, 32 individuals reported a total of 47 consequences. After the third vaccination, 33 individuals reported a total of 43 consequences. Table 7 breaks out the different work and medical related consequences and reflects that decreased activity and a follow-up clinic visit were the most commonly reported consequences. On one AIMN, "hospitalization" was checked following the first immunization (captured under "other" in Table 7). The clinician (CC) at Camp Casey confirmed that, in this instance, a female soldier vaccinated at an outlying clinic supported by Camp Casey was referred to Camp Casey's emergency room to have her arm checked. A

Table 7
Descriptive summary of reported significant consequences to adverse events

	Number reported	Description
Following first vaccination: $N = 42$ of 813; total reported consequences = 60		
Less active	34	Duration 1–17 days, mode 2 days, median 3 days
Duty limited	6	Duration 1–7 days
Lost work	4	Duration 0.5–2 days
Used meds	3	Duration 1–4 days
Visited clinic	9	Follow-up only
Other consequences	4	ER visit with follow-up (see text), temp decreased arm strength
Following second vaccination: $N = 32$ of 773; total reported consequences = 47		
Less active	26	Duration 1–7 days, mode/median 3 days
Duty limited	1	Duration 1 day
Lost work	4	Duration 1 day
Used meds	1	Duration 10 days
Visited clinic	12	Follow-up only
Other consequences	3	Temporary decreased number of push-ups
Following third vaccination: $N = 33$ of 461; total reported consequences = 43		
Less active	28	Duration 1–14 days, mode/median 2 days
Duty limited	4	Duration 2–3 days
Lost work	4	Duration 1–2 days
Used meds	1	Duration 10 days
Visited clinic	6	Follow-up only
Other consequences	0	

sterile abscess had developed at the immunization site. The soldier was followed-up at Camp Casey and the abscess resolved without sequelae. A vaccine adverse event reporting system report was generated. Further immunizations were deferred. For Camp Casey, this was the most serious consequence noted. In all but one other case (of decreased activity lasting 17 days following the first immunization), adverse consequences resolved well under 2 weeks with most resolving within a few days.

4. Discussion

Accurate knowledge of soldier experience is important when attempting to establish trust with soldiers in a mandatory immunization program. Many soldiers experience adverse events following AVA immunization, with nodules and injection-site erythema most common. The AIMN included only variables found on the existing AVA package insert and important in making a decision whether to immunize the soldier as planned, thus justifying the need to collect self-reported information on health status, medication use, adverse events, and adverse event consequences associated with the vaccine [11]. Care was exercised to keep the AIMN brief, simple to complete, and easy to use. By allowing soldiers to check "other" and provide comments, it is also possible to identify other adverse events that might not have been mentioned in the insert or local AVA vaccination guidelines, such as headaches, hives or generalized urticaria. Within the comment section, women reported the use of BCMs that accounted for much of the medication used, and allowed better discrimination of the potential effect NSAIDs may have to adverse event reporting. Differing types of BCMs (pills or implants) were frequently written into the comments so that an ad hoc analysis of the impact BCMs might have on adverse events was possible. This analysis found no association between use of BCMs and reporting of adverse events among females.

Within the multivariate analysis, logistic regression and CHAID findings differ slightly. This relates to both the modeling approach and management of missing variables. The logistic regression model selected cases that had all potential independent variables, or potential risk factors, of interest so that each potential risk factor could be controlled relative to the contribution of each potential risk factor to the outcome of interest. Cases with missing values were dropped and the regression results were used to identify the percent of variance in outcome related to the risk factors. The model reflects risk factor odds ratios. There is no assurance that there is any population within the analyzed group that has all risk factors. The CHAID analysis attempts to create specific population groups with specific potential risk factors that are as different as possible relative to the outcome of interest. Cases with missing variables can be considered and grouped with the population that is otherwise similar. Thus, more cases can be used in the analysis. Logistic regression identifies the odds ratio for each risk factor to the outcome of interest while the CHAID analysis identifies population segments that have a specific probability for that outcome.

Several explanations for gender differences are plausible, including differential inflammatory responses to antigenic stimuli, the effect of circulating hormones, and the survival advantage to offspring of an enhanced immune responsiveness in women. The positive correlation between adverse event reports and NSAID use is unexpected and could be a spurious finding. Clinically, use of NSAIDs prior to a vaccination would be expected to ameliorate adverse events. However, in the implementation of the vaccine program, NSAID pre-treatment was not within the general guidance. Immunological factors that might be connected to NSAID use and increased reactivity remain speculative. Evidence for the relative contributions of these or other explanations remains to be gathered.

We attribute the large fraction of injection-site reactions to subcutaneous administration of an aluminum-adjuvant containing vaccine. Aluminum in vaccines was the focus of a workshop sponsored by the National Vaccine Program Office in May 2001. Safety, rationale, mechanisms of action, and research directions were discussed, with one panel publishing what was known and a second panel describing what needed additional research. They identified no clear aluminum dose-response relationship to severe erythema, but route and timing appeared to be important factors. In terms of quantity of injected aluminum, AVA on single doses is well within recommended safety ranges, but a full series with boosters given over a military career results in a relatively large amount of injected aluminum. The mechanisms are unknown but there are several credible models that also include route of administration and gender that explain the impact of aluminum adjuvant on the immune system [27–32]. Gender, prior AVA adverse events, NSAID medication, and minor health problems might be surrogates for individual immunological system reactivity that is enhanced by the SC injection of aluminum adjuvant. Anthrax vaccine is the only licensed vaccine that still calls for SC dosing, without any mention of intramuscular (IM) injection [8,33]. Both the dosing route and schedule has become a focus for research for both the Army and CDC, based upon noted gender differences and increased reactogenicity of the SC route over an IM route [24,33,34].

Pittman et al. noted adverse event rate differences in his large-scale study of short-term safety of anthrax vaccine [35]. The study relied on follow-up clinic visits for a chief complaint of an adverse event among 1583 volunteers over a 25-year period, using vaccine from 18 lots. Medical record extracts revealed an overall 1% systemic and 3.6% local adverse event reaction rate. Reported percentages are inconsistent with the magnitude of adverse consequences reported in this analysis, possibly reflecting a magnitude of difference between the occurrence of a noticeable adverse event and the decision to bring that event to the attention of a health care provider who then clearly records the visit in an extractable

free-text medical note. However, the magnitude of adverse event reports and consequences are consistent with a more recently published research study by Wasserman et al. of 601 health care workers who received all six immunizations over 18 months [36]. This analysis takes advantage of the fact that by nature of the program, age range, immunization schedule, and lot number were held relatively constant, thus maximizing the potential to detect adverse event and consequence differences that might be related to gender, current medication use, and minor health problems.

These data reflect a higher percent of injection-site and systemic adverse events than are reported in the package insert. Use of the AIMN for capturing adverse events and concerns is perhaps the most sensitive and inexpensive observational method to capture data related to safety. Currently, the standard approach for capturing information with this level of sensitivity would be through a research protocol where individuals are asked to volunteer information not normally part of the medical documentation process [36]. The current clinical documentation standard is also the least sensitive method to collect adverse event information using VAERS. The standard method relies on additional reporting requirements through VAERS that will highlight a significant adverse consequence of the small subset of the population experiencing an adverse event. In the middle is a method that relies on individuals returning to a medical clinic to report concerns on a prior immunization, with documentation written into the medical record [35].

4.1. Limitations

A single TMC, located in a field setting, was the only site using this note, creating a significant data-capture limitation. All soldiers receiving an immunization at this TMC completed the AIMN. The AIMN was an additional effort over normal documentation processes that included entering data into an electronic immunization tracking system. The absence of an AIMN only reflects that the AIMN was not filled out. Although most personnel assigned to units covered by this TMC would receive their immunizations at this TMC, not all individuals received all four shots at this specific TMC. Although much of the analysis can use information from one note, when it is necessary to link notes, a significantly lower number of cases are included. This is especially true between the third and fourth immunizations, where the time interval is longer than between earlier doses. However, should this approach become a standard for medical documentation, the acute experience of this group would establish a baseline for long-term outcome evaluation.

Our approach is susceptible to recall bias when one considers that less time passes between the first three immunizations (2 weeks), compared to the interval between the third and fourth immunization (5 months). Although it might be possible to conclude there are fewer adverse events related to the third immunization, review of the substantial decline in "other" adverse events reported and the relative percentage increase in the number of adverse consequences among those reporting adverse events would indicate presence of recall bias.

Differences related to gender probably does not reflect a selective reporting or information bias, to the extent women might be more prone to report an adverse event. Wasserman et al. report a possibility of a healthy worker bias and reflect no evidence of bias related to gender in their analysis [36]. In this analysis, equivalent percentages of men and women report a work or medically related consequence of an adverse event, indicating that both are reporting all events at the same relative level of sensitivity. Had information bias been present, it might present as a differential in reporting of significant adverse consequences among the pool of men and women reporting one or more adverse events. With comparable percentages reporting adverse consequences by gender, such an effect is unlikely. Relatively high percentages of adverse event reports with a low level of significant adverse consequences seem to reflect a high level of comfort soldiers had filling out the AIMN, knowing the information would be used as intended, to help providers make immunization decisions, document the soldier's experience, and serve as a communication tool between soldier and provider to answer concerns and questions.

From this group, one VAERS report was generated from an adverse event that captured clinical concern. Designed to detect adverse events that reach a significant threshold, such as hospitalization, or an event that otherwise concerns either patient or provider, VAERS has been found to be useful for post-marketing sentinel surveillance, potentially triggering the need to reassess the vaccine or for additional research [37,38]. The percentage of adverse events derived from VAERS is expected to be less than adverse events experienced. Within the military, events such as lost duty days or follow-up clinic visits could have triggered a VAERS report for use in the decision whether to exempt the soldier from further immunizations. However, in a context of ambient illness rates, lost duty days or clinic visits are relatively common compared to the number of recalled consequences soldiers related to the prior immunization. The AIMN also allowed capture of patient concerns, adverse events, and consequences. Any adverse consequence would be reviewed at the time of the next scheduled immunization. Use of the AIMN would permit automated generation of VAERS reports as a function of severe or unexpected consequences that were also recorded on the AIMN.

5. Conclusions

Previously, adverse events had not been stratified by gender, health status, medication use, and prior vaccine experience for anthrax vaccine. This paper, through an evaluation of rapidly completed structured anthrax immunization medical notes at one military clinic, highlights a

larger percentage of adverse events than reflected in the vaccine package insert, especially among women. The AIMN allowed generation of a safety profile that demonstrates individual variability as a function of gender, past experience with the vaccine, and concurrent medication use. Most events have minor transient consequences. From this group, one VAERS report was generated. The AIMN is an effective tool for collating the clinical experience of large groups. Medical notes can be re-engineered to be efficiently used for both patient management and outcomes management. This concept is being integrated into the military's approach to the current smallpox vaccination program.

6. Disclaimer

The views represented within this paper are those of the authors alone, and should not be construed to represent the official or unofficial views of the Department of Defense or any other government agency.

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